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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TAROLLI, SUNDHEIM, COVELL & TUMMINO, LLP
1300 EAST NINTH STREET
SUITE 1700
CLEVELAND, OH 44114

EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,528	BROWN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7,8,15 and 26-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7,8,15 and 26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed July 21, 2010 (hereinafter referred to as "the response") has been entered. No amendments have been made.

Accordingly, Claims 4, 7, 8, 15, and 26-39 remain pending in the instant application and are examined herein.

The location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Anne-Marie Falk, Ph.D. in Art Unit 1632. The Examiner's contact information is provided below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 7, 8, 15, and 26-39 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth at pages 6-11 of the Office action of March 27, 2007, at pages 3-7 of the Office action of December 10, 2007, in the advisory action of May 6, 2008, at pages 2-4 of the Office action of March 17, 2009, in the advisory action of November 18, 2009, and at pages 2-6 of the Office action of January 21, 2010, because the specification, while being enabling for a method of inducing apoptosis in cultured cancer cell lines, comprising the step of introducing into said cells *in vitro* an expression vector comprising a nucleic acid encoding a human KChAP protein as set forth in SEQ ID NO: 2, said nucleic acid operably linked to a promoter active in cancer cell lines, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent Claim 4 is directed to a method for inducing apoptosis in human prostate cancer or breast cancer cells comprising:

delivering to and expressing in said cells a nucleic acid comprising:

i) a nucleotide sequence encoding human KchAP protein; and

ii) a promoter active in said cancer cells, wherein the promoter is operably linked to the sequence encoding said protein, wherein said cancer cells are in a tumor in a subject, and wherein said nucleic acid is in a viral vector which is delivered to said cancer cells by intratumoral injection.

As previously indicated, the specification is considered enabling for a method of inducing apoptosis in cultured cancer cell lines, comprising the step of introducing into said cells an expression vector comprising a nucleic acid encoding a human KChAP protein as set forth in SEQ ID NO: 2, said nucleic acid operably linked to a promoter active in cancer cell lines.

The previous Office actions indicated that the claims, when given their broadest reasonable interpretation in view of the as-filed specification, are directed to a method of inducing apoptosis in human prostate cancer cells or breast cancer cells in a tumor in a subject, following delivery of a viral vector expressing the human KChAP protein, by intratumoral injection. Therefore, the claims broadly embrace a method of tumor cancer therapy.

At pages 2-4 of the response, Applicants allege that only routine experimentation is needed to enable the full scope of the claims. Citing the decision of *In re Wands*, Applicants note that even a considerable amount of experimentation is not undue if it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the expermentation should proceed. Applicants go on to allege that the specification provides guidance and direction to the skilled artisan commensurate with the scope of the claims. Applicants assert that the specification teaches that apoptosis

can be induced in prostate cancer cells or breast cancer cells by delivering and expressing a nucleic acid encoding human KChAP protein, in a viral vector, via intratumoral injection. Specifically, Applicants point to the specification at paragraphs 0047, 0070, 0062, 0063, and 0075. Applicants go on to point out that the specification notes that the present method is especially useful for treating a patient with an epithelial carcinoma, such as breast cancer or prostate cancer, and that the specification notes that apoptosis may be induced in cancer cells, particularly prostate cancer cells, by introducing a KChAP protein into the cell. Applicants further point out that the specification notes that polynucleotides comprising a coding sequence for KChAP protein can include a promoter that permits expression of the protein, and that viral vectors may be used to deliver the KChAP polynucleotides to the cell. Finally, Applicants point out that the specification notes that delivery of the KChAP polynucleotide may be via intratumoral injection. With regard to the working examples presented in the specification, Applicants assert that the examples demonstrate that delivery and expression of a nucleotide sequence encoding human KChAP protein induces apoptosis in human prostate cancer and breast cancer cells. Applicants provide a summary of Examples 1-4 (paragraph bridging pages 4-5 of the response) and conclude that, taken together, the examples demonstrate that delivery and expression of a nucleotide sequence encoding human KChAP protein induces apoptosis in both prostate cancer cells and breast cancer cells.

In response, the prior Office actions did acknowledge the teachings of the specification, and particularly the working examples, which pertain to subcutaneous xenograft tumors implanted into immunodeficient mice. However, in view of an analysis of the *Wands* factors, the evidence of record would lead one to conclude that, at the time of the invention, the skilled artisan would have been required to engage in undue experimentation to enable the full scope of the claims, which include the treatment of immunocompetent animals with spontaneous tumors. The prior art teachings of Kerbel et al. (1999), Vieweg et al. (1995), and Hoffman et al. (1999) were cited to demonstrate that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically (usually

subcutaneous) grown counterparts, and that the animal model exemplified in the instant specification, i.e. subcutaneously-growing human cancer cell lines in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity. Moreover, a cancer cell line is not comprised of a mixture of cancer cells and normal cells, and in view of the additional issues previously highlighted, such delivery would likely also produce deleterious undesired consequences with respect to the promotion of unwanted cell proliferation.

At pages 5-6 of the response, Applicants allege that the animal models used in the present application do sufficiently represent clinical cancer. Applicants assert that a more recent article authored by Kerbel (Kerbel 2003) discusses the pros and cons of different animal models of human carcinoma and represents that the xenograft animal model used to support the claimed invention is sufficient to reflect human carcinoma and that the alternate models argued in the Office action as preferred models, over the xenograft model, have drawbacks. Applicants' arguments pertaining to Kerbel 2003 have been fully considered, but are not deemed persuasive, in view of the evidence of record as a whole. With regard to Kerbel 2003, however, the prospective data that is referred to in the article pertains to the predictive value of preclinical studies on cytotoxic chemotherapeutic drugs. It is maintained, as previously indicated, that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient mouse fails to reflect human carcinoma, which necessarily involves treatment of an immunocompetent animal. Additional issues relate to the use of cell lines (as opposed to primary tumor cells) and ectopic and heterotopic transplantation of said cell lines (versus orthotopic transplantation or primary tumor cells) in immunodeficient nude mice, constituting deficient cancer models, as well as the paradox that enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis, but also tumor cell proliferation, especially in a tumor mass comprising a mixed cell population, bringing into question the validity of the claimed method as a therapeutic, and specific teaching away from Applicants' claimed invention by the prior art of Wang (Eur. J. Physiol. 448:274-286; 2004) which states: "K^+ channels favor

tumor cell proliferation, therefore, inhibition of K^+ channel function or down-regulation of K^+ channel expression should inhibit tumorigenesis…On the other hand, K^+ channels also promote apoptotic cell death…enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers" (paragraph bridging pages 281-282).

At pages 7-8 of the response, Applicants disagree with the Office's characterization of Wang (2004). Applicants submit that the Examiner has improperly broadened the claimed invention to include the expression of all K+ channels in general. Applicants note that KChAP functions to boost expression of a subset of K+ channels and that Wang makes no reference to KChAP as being pro-oncogenic. At pages 8-10 of the response, Applicants allege that the statements of Shieh are used out of context and does not actually support the Office action's assertion of the unpredictability of the claimed invention. However, the evidence of record on the whole argues against the overexpression of K^+ channels, as such is known to promote malignancy. The state of the art with regard to potassium channels as potential therapeutic targets, at the time of the invention, is reviewed by Shieh et al. (Pharmacol. Rev. 52:557-593; 2000). The authors describe KChAP as a chaperone protein, or auxilliary factor, regulating the function and expression of some of the Kv channels, such as Kv2.1, Kv1.3 and Kv4.3, and state that given the diversity of K^+ channel subunits, understanding the composition of channel complexes *in vivo* remains a challenge (first column, p. 566). Shieh et al. additionally state that K^+ channel activities play important roles in signal transduction pathways leading to proliferation, differentiation and cell fusion (second column, p. 574), that enhancement of current is directly involved in apoptosis and oncogenesis (first column, p. 575), and that overexpression of rEAG K^+ channels in Chinese hamster ovary or NIH 3T3 cells induces significant features characteristic of malignant transformation (second column, p. 575). The authors conclude that key hurdles in targeting K^+ channels remain to be resolved (second column, p. 577). Thus, the prior art of Shieh et al. highlights the unpredictability with regard to targeting K^+ channel

expression, and together with the post-filing art of Wang et al. argue against the overexpression of K^+ channels, as such is known to promote malignancy.

In determining whether a specification is enabling, the factors to be considered include the presence or absence of working examples, the nature of the invention, the state of the prior art and the predictablility or unpredictablility of the art. The working examples cited by Applicants are not commensurate in scope with the claimed invention and are directed to using cell lines, that in turn fail to reflect the issues raised for normal breast and prostate tumors, comprising a mixture of normal and transformed cells. As also indicated in MPEP 2164.03, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). The working examples embody a number of deficiencies that do not allow one of skill in the art to extrapolate their teachings to applications wherein a cancerous tumor may be treated in a subject. The evidence of record as a whole indicates that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient nude mouse fails to reflect human carcinoma, and therefore a person of skill in the art would need to carry out further experimentation, with an uncertain outcome and constituting undue experimentation to introduce a viral expression vector encoding KChAP, to be effective in inducing apoptosis and or treating a subject with prostate or breast cancer *in vivo*.

Applicants' reference to *In re Brana*, that in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development, ignores the critical *Wands* factor of predictability, that must be considered in an enablement rejection. Further experimentation is permissible when it is merely routine and predictable; however, in the instant case, enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis, but also tumor cell proliferation, and as the unpredictability in targeting K^+ channels, and the teaching away from their overexpression has been made of record by factual evidence, Applicants' allegations to the contrary notwithstanding.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues stating that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005); "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." The claimed methods of delivery and overexpression of KChAP protein constitute such a "germ of an idea". Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Accordingly, the rejection is maintained for Claims 4, 7, 8, 15, and 26-39 for reasons of record and the foregoing response.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632